DETAILED ACTION

1. The Amendment filed December 18, 2009 in response to the Office Action of November 24, 2009, is acknowledged and has been entered. Claims 1-10 and 16-30 are pending. Claim 3 is amended. Claims 11-15 are canceled. Claims 26-30 are new. Claims 6, 7, 10, 20-25 remain withdrawn. Claims 1-5, 8, 9, 16-19, and 26-30 are currently being examined as drawn to the elected species of breast cancer, breast tissue, and surgery.

New Rejection

(based on new considerations)

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-5, 8, 9, 16-19, and 26-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some

experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claims are drawn to a method of ameliorating a symptom of a prolactin receptor-related condition in a subject in need of such amelioration, comprising: administering to said subject a human growth hormone-based prolactin receptor antagonist and zinc in an amount effective to ameliorate said symptom (claim 1), a method of treating a prolactin receptor-related condition in a subject in need of such treatment, comprising: administering to said subject a human growth hormone-based prolactin receptor antagonist and zinc in an amount effective to treat such condition (claim 2), a method of reducing the risk that an individual will acquire a prolactin receptor-related condition comprising: administering to said individual a human growth hormone-based prolactin receptor antagonist and zinc in an amount effective to treat

such condition (claim 3), the method of Claim 1, 2, or 3 wherein the condition is breast cancer (claims 4, 5, 6), wherein said antagonist is administered to a tissue with an effective local concentration of zinc (claim 8, 16-19), the method of claim 1, 2, or 3, wherein the human growth-hormone-based prolactin receptor antagonist is a human growth hormone comprising a single amino acid substitution selected from F10A, N12A, … and S18A (claim 26), the method of claim 1, 2, or 3, wherein the human growth-hormone-based prolactin receptor antagonist comprises E56D/R64M or F176Y/I179T amino acid substitutions (claim 27), the method of claim 1, 2, or 3, wherein the human growth-hormone-based prolactin receptor antagonist comprises I4A/L6A/G 120A, I41/L6A/G 120A/T 123A, F 1A/I4A/G 120UT 123A, F1A/I4A/G120F, or F1T/I4F/L6R/G120R/T123D amino acid substitutions (claim 28), the method of claim 1, 2, or 3, wherein the human growth-hormone-based prolactin receptor antagonist comprises Y11V/L113I/K115E/D 116Q/E118K/E119R/G120L/Q122E/T 123G/G126L/R127I/E129S, … and F97R/A98G/N99M/SIOOQ/LIO1D/VIO2A/YIO3P/GIO4E amino acid substitutions (claim 29), the method of claim 1, 2, or 3, wherein the human growth-hormone-based prolactin receptor antagonist is attached to poly(ethylene glycol) (claim 30).

The specification discloses that a “prolactin receptor-related condition” refers to a condition affected by either systemically or locally increased prolactin concentrations or activity, or locally increased prolactin receptor number or activity, and examples include cancers such as breast tumors (p. 7-8, [0030]). The specification discloses that a growth hormone-based prolactin receptor antagonist refers to a factor which neutralizes,

impedes, or otherwise reduces the action or effect of a prolactin receptor. Generally, the factor is one that binds to a prolactin receptor or a growth hormone receptor with a higher affinity in the presence of zinc than in its absence. The growth hormone-based prolactin receptor antagonist can be any molecule that binds the prolactin receptor with a higher affinity in the presence of zinc than in its absence and inhibits prolactin receptor activity that is known to one of skill in the art without limitation. Any growth hormone-based prolactin receptor antagonist can be used according to the methods of the invention. The specification lists non-limiting examples of growth hormone-based prolactin receptor antagonists including numerous mutants of human growth hormone (p. 9-10, [0039]; p. 16-20, [0068-0080]). The specification provides only prophetic examples for treating breast cancer, prostate diseases, and hyperprolactinemia with a "growth hormone-based prolactin receptor antagonist" and zinc (p. 46-53).

One cannot extrapolate the disclosure of the specification to the enablement of the claims because the specification does not provide guidance or examples for any "growth hormone-based prolactin receptor antagonist" functioning to predictably treat, reduce the risk of, or ameliorate a symptom of any "prolactin receptor-related condition" in the presence of zinc as claimed. Although the specification contemplates numerous mutants of human growth hormone that could function to treat, reduce the risk of, or ameliorate a symptom of any "prolactin receptor-related condition," the specification fails to provide any working examples demonstrating that any of the contemplated mutants of human growth hormone can predictably function to treat, reduce the risk of, or

ameliorate a symptom of any prolactin receptor-related condition including breast cancer.

The art teaches that different types of mutations in human growth hormone (hGH) have different effects on cells expressing prolactin receptor in the presence of zinc, and hGH mutant G120R can actually increase cancer cell growth in the presence of zinc. For example, as taught by Fuh et al (US Patent 6,429,186) and as argued by Applicants on pages 6-11 of the remarks, the addition of zinc to G120R when contacted with breast cancer cells *in vitro*, resulted in increased 3H-Thymidine incorporation, as compared to G120R alone (Figures 16, 17a, and 18), demonstrating that the rate of proliferation of the breast cancer cells actually increases in the presence of G120R with zinc. As Applicants argued, given the teaching of Fuh et al '186, there is no reasonable expectation of success to treat, reduce the risk of, or ameliorate a symptom of a prolactin receptor-related condition in a subject (p. 9-10 of Remarks, bolded and underlined). Applicants also argued that Fuh et al (J of Biological Chemistry, 1995, 270:13133-13137) teach there is variability in prolactin receptors among breast cancer cell lines, wherein an anti-hPRL receptor antibody was able to inhibit growth of MCF-7 breast cancer cells but not BT-474 breast cancer cells (Figure 4), hence no meaningful conclusion can be made from Fuh et al (1995) with respect to any effect of an hGH-based prolactin receptor antagonist and zinc on growth of an actual breast cancer cell. Applicants stated that one skill in the art would not have a reasonable expectation of success based on the data presented in Figure 3D of Fuh et al (1995) with respect to G120R-hGH alone or in combination with $ZnSO_4$ (p. 10 of Remarks).

Additionally, Dattani et al (J Biological Chemistry, 1995, 270:9222-9226) teach that human growth hormone mutant G120R acts as an antagonist of native hGH, but can also act as an agonist to generate intracellular signals leading to metabolic activation and proliferation of Nb2 cells (rat lymphoma cells). Dattani et al teach that in recent *in vivo* studies it has proved difficult to demonstrate that antagonist activity of G120R on growth in the rat and the data was compatible with a weak but significant agonist activity in the absence of GH, via rat PRL receptors (p. 9223, col. 1). Dattani et al report that G120R stimulates Nb2 cells in the MTT-ESTA bioassay and G120R is classified as both an agonist and antagonist, and its sensitivity to zinc may be able to explain its variable activity (p. 9223, col. 1; p. 9225, col. 2; p. 9226, col. 2). Dattani et al demonstrate that different concentrations of zinc can alter the effect of G120R to be antagonistic or agonistic (Figure 3, 4; p. 9224, col. 2). Dattani et al further teach that although binding of G120R to the receptor may be compromised, G120R can actually interact with lactogenic receptors and stimulate target cells if present at a high enough concentration (p. 9226, col. 1). Dattani et al teach it has proved difficult to establish significant hGH antagonism *in vivo* in the rat, and the present results confirm that PRL agonist activity occurs at far lower doses than those necessary to antagonize hGH at the rat Nb2 PRL receptor and that *in vivo* studies in which G120R is used as a specific GH antagonist in the rat may need to be interpreted with caution (p. 9226, col. 2). Hence, Dattani et al teach the unpredictable extrapolation of even their *in vivo* rat studies to the function of G120R in humans. Duda et al (Protein Engineering, 2003, 16:531-534) teach that the addition of zinc had different effects on hGH based prolactin

receptor antagonists because the antagonists possessed different mutations. The type of mutation each hGH mutant had determined whether zinc would reduce or enhance the biological activities of the hGH mutants (p. 534, col. 1; Table I; Figures 1 and 2). Given the teaching of Duda et al for the differing effects of zinc on different hGH mutants, one of skill in the art could not predictably treat, reduce the risk of, or ameliorate a symptom of any prolactin receptor-related condition in a subject comprising administering any hGH based prolactin receptor antagonist and zinc as claimed. A high quantity of experimentation would be required to determine which human growth hormone based prolactin receptor antagonist would predictably function to treat, reduce the risk of, or ameliorate a symptom of what prolactin receptor-related condition and in the presence of zinc.

Therefore, in view of the state of the art, the quantity of experimentation necessary, the breadth of the claims, lack of guidance in the specification, and the absence of working examples, it would require undue experimentation for one skilled in the art to practice the invention as claimed.

3. All other rejections recited in the Office Action mailed November 24, 2009 are hereby withdrawn in view of amendments and arguments.

4. **Conclusion:** No claim is allowed.

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA B. GODDARD whose telephone number is (571)272-8788. The examiner can normally be reached on 7:00am-3:30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Laura B Goddard/
Primary Examiner, Art Unit 1642